REMARKS

Claims 1, 14-16, 19 and 21-30, 32, 33, and 37-44 are under consideration in this case- encompassing Group II (except that the Examiner has included claim 1) with an election of the species BABA as the alkylating agent, phosphine as the disulfide reducing agent, alkaline phosphatase as the "activating agent" and an antibody "as the reagent capable of specifically binding to modified homocysteine

§112, First Paragraph

The Examiner rejected all pending claims as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed, had possession of the claimed invention. Specifically the Examiner states that the current claims refer to "derivatizing haloketones and haloaldeheyes and the properties of the protecting group (e.g. 'renders alkylating agent . . on the protected functional group')" lack support.

Applicants traverse. To clarify, the claims to not state "derivatizing haloketones or haloaldehydes". Instead, the claim language is structural - "derivatized haloketones or haloaldehydes" (e.g. substituted). The amendment is supported throughout the specification. The specification primarily uses the term "protected" and the specification is replete with such references. However, the term derivatized is described at page 20, line 10 to page 22, line 10 and in particular page 21, lines 21-23 and page 22, lines 3-18 (using "substituted").

With reference to the properties of the protected functional group, Applicants point to pages 1-3. Applicants have substituted the term "physiological" for "biological". Thus, the reference to the properties of the protected alkylating agent can be found at page 1, lines 1-35 and page 2, lines 17-20, page 10, lines 1-15, and page 21, lines 3-5. While Applicants have amended the claims, Applicants point out that the title and indeed the invention is directed at "Protecting Groups for Biological Labeling".

Applicants respectfully submit that the amendments are supported in the specification and request that the rejections be withdrawn.

§112, Second Paragraph

The Examiner rejected all claims as being indefinite.

In points A-C, the Examiner states that claims 1, 19, 32 and 44 are confusing as to whether an alkylating reagent is for example, a haloketone, or some derivative, what part of the alkylating agent constitutes the "functional group" and what portion of the alkylating agent is being derivatized. Applicants have amended the claim to insert "the carbonyl". See, examiner's response dated May 3, 2002 suggesting the same.

In point D-F, the Examiner rejects claim 1 stating that the "reactivity and nonreactivity" is indefinite, that "nucleophilic or sulfhydrly group" is confusing, and the metes and bounds of the "types of reactions" is lacking.

Applicants traverse. In *In re Barr* 444 F.2d 588 (CCPA 1971) the court reviewed similar language. The court held that "incapable of forming a dye with said developer agent" was perfectly acceptable and set definite boundaries as to what patent protection was sought. See MPEP 2173.05(g) The claim is reasonably definite as to apprise one of skill in

the art of the invention claimed and the requirements of the statute have been met.

§102(b)/§103 Rejections under Schepin et al.

The Examiner rejects claim 1 under §102(b) or alternatively under §103 in view of Schepin et al. Zhurnal Organicheskoi Khimii (1990) Vol. 26 (11) pages 2394-2397 (and RN 13654-49-4 and RN 1365432-5).

First, the Examiner states that amended claim 1 can be interpreted as a product-by-process claim. Applicants are claiming a composition.

Schepin does not disclose an alkylating agent having a carbonyl of a haloketon or alpha haloaldehyde functional group substituted with a protected functional group.

§102(b,e) Rejections under Metzger

Claims 1 and 14 were rejected as being anticipated by Metzger and if necessary further in view of Morrison & Boyd and Caplus Abstract No. 1947:25587. With respect to claim 1, the Examiner states that Metzer discloses a "protected alkylating agent" of formula III (col. 2, line 45) and with respect to claim 14, that Metzger also discloses a "disulfide reducing agent" (e.g. ZN in HCL/H2SO4).

With respect to claim 1, Formula III of Metzger does not contain an alkylating reagent having a haloketone or alpha haloaldehyde functional group said alkylating reagent having the carbonyl of its haloketone or haloaldehyde functional group derivatized with a protected functional group. As stated in the claim the protected functional group renders the alkylating agent, when under physiological conditions, unreactive to a nucleophilic or sulfhydryl group and reactive to a nucleophilic or sulfhydryl group, when

under physiological conditions, by action of an enzyme on the protected functional group. None of these features are disclosed or suggested by Metzger.

As discussed in the prior response, to the contrary and as is shown by Metzger, Formula III when in the presence of a nucleophilic group reacts with the nucleophilic group. It is unprotected and does not have the functional group used for alkylation derivatized with a protected functional group as required by the present claims. For instance, in Formula II a nucleophilic group (a sulfhydryl) will form upon contact with a strong reducing agent such as the Zn/acid mixture. Upon forming the nucleophilic group from the compound of Formula II, the nucleophilic group reacts with the compound in Formula III to form the compound in Formula I. In complete contrast, substituting the composition of claim 1 for Formula III there would be no reaction with a nucleophilic group generated from Formula II from the action of the Zn/acid mixture because the compositions of claim 1 comprises an alkylating agent that comprises a "protected functional group" not found, disclosed, or even suggested by Metzger.

The same applies to the other claims. Even in the presence of a reducing agent such as the Zn/acid mixture the "protected functional group" remains protected. This is neither taught nor suggested by Metzger.

Thus, Applicants urge that the Examiner withdraw the rejection.

102(b) Rejections under Van Atta

Claims 1, 14-16, 19, 21-30, 32, 33, and 27-44 stand rejected as being anticipated by Van Atta.

The Examiner states that Van Atta discloses compositions, kits and assays for performing immunodetection

of homocysteine - both homogeneous and heterogeneous and that Van Atta discloses "modifying reagents, especially "alkylating reagents' and preferentially BABA. The examiner states that BABA (e.g. example IV) and a modified BABA (e.g. BABA-N-hydroxysuccinamide ester at col. 21) are "protected alkylating agents" within the scope of the claimed invention. In addition the Examiner states that Van Atta also discloses "releasing agents" particularly "disulfide reducing agents". Thus, the Examiner concludes that claims 1 and 14-16 which merely require a "protected alkylating reagent alone or further combined with a disulfide reducing agent" (e.g. TCEP). Applicants respectfully traverse the rejection.

Applicants claim a alkylating reagent, that is as currently recited: a composition comprising an alkylating reagent alkylating reagent having a haloketone or alpha haloaldehyde functional group said alkylating reagent having the carbonyl group of its haloketone or haloaldehyde functional group derivatized with a protected functional group. The protected functional group renders the alkylating agent, when under physiological conditions, unreactive to a nucleophilic or sulfhydryl group and reactive to a nucleophilic or sulfhydryl group, when under physiological conditions, by action of an enzyme on the protected functional group.

Van Atta does not disclose an alkylating reagent that has a protected functional group. Van Atta instead discloses the opposite. With reference to BABA: When BABA is in the presence of a nucleophilic group (e.g. reduced homocysteine) the BABA reacts with the free Hcy. See Van Atta at column 29, lines 60 to column 30, lines 35. Thus, BABA is not an alkylating reagent having the metes and bounds set out in Applicants' claims. It is not unreactive

to a nucleophilic group when in the presence of such nucleophilic group. The same holds true for BABA-NHS. Van Atta at column 22, line 15 describes the reaction of BABA-NHS with BSA, which in the presence of DMSO forms BABA-activated BSA. In turn the BABA-activated BSA reacts with homocysteine. See column 22, lines 14-59. In contrast, a protected-BABA would not react with a nucleophilic group until the protected functional group was deprotected. Thus, Van Atta does not disclose or suggest the present invention. Further, Applicants note that the use of alkaline phosphatase as discussed in Van Atta at col. 21-23 and throughout Van Atta has nothing to do with using alkaline phosphatase to "deprotect" a "protected" alkylating reagent as claimed by Applicants. Van Atta does not disclose alkylating reagents that have a protected functional group capable of reacting with a nucleophilic group when deprotected wherein the protected functional group is unreactive to a nucleophilic group when in the presence of a nucleophilic group. There is nothing the alkylating reagents disclosed in Van Atta that could be "deprotected" by alkaline phosphatase. Thus, Applicants respectfully request that the rejections under Van Atta be likewise withdrawn.

Nonstatutory Double Patenting Rejections under Van Atta

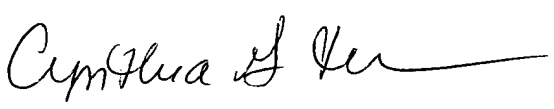
Claims 1, 14-16, 19, 21-30, 32, 33, and 27-44 stand rejected under the judicially created doctrine of double patenting over claims 1-29 of U.S. 5,478,729 (Van Atta). Applicants note that claim 46 has been cancelled.

Applicants submit that the claims are not obvious in view of Van Atta for the reasons discussed above. Van Atta neither discloses nor suggests the protected alkylating

reagents defined by the claims as amended. In contrast to the present invention the alkylating reagents disclosed by Van Atta react with nucleophilic groups. Thus, Applicants respectfully request that the rejection be withdrawn.

If the Examiner believes that a telephone call to the undersigned would clarify any issue, Applicants respectfully invite the Examiner to contact Applicants attorney at the phone number given below.

Respectfully submitted,



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AMENDMENTS TO THE CLAIMS (Marked to show changes)

Claim 1 (twice amended). A composition comprising an alkylating reagent having a haloketone or alpha haloaldehyde functional group said alkylating reagent having its carbonyl group of the haloketone or alpha haloaldehyde functional group derivatized with a protected functional group wherein said protected functional group renders the alkylating agent, when under [biological] physiological conditions, unreactive to a nucleophilic or sulfhydryl group and reactive to a nucleophilic or sulfhydryl group, when under [biological] physiological conditions, by action of an enzyme on the protected functional group.

Claim 19 (twice amended). A kit for use in a method for detecting and determining the amount of homocysteine in a sample, comprising in a packaged combination: a first reagent comprising an alkylating reagent having a haloketone or alpha haloaldehyde functional group, the carbonyl of said haloketone or alpha haloaldehyde functional group derivatized with a protected functional group said protected functional group capable of reacting with the sulfhydryl group of homocysteine to form modified homocysteine when said protected functional group is deprotected, a second reagent comprising an activating reagent capable of deprotecting said alkylating reagent by removal of the protected functional group, and a third reagent capable of specifically binding to said modified homocysteine, each in an amount sufficient to conduct at least one assay.

Claim 32 (amended). A method of determining the amount of homocysteine in a sample suspected of containing said homocysteine, comprising the steps of :

(c) bringing together in an aqueous medium:

(5) said sample,

(6) a first reagent comprising an alkylating reagent having a haloketone or alpha haloaldehyde functional group, the carbonyl of said haloketone or alpha haloaldehyde functional group derivatized with a protected functional group capable of being activated to chemically modify the sulfhydrly groups of homocysteine to form modified homocysteine, and

(7) a second reagent comprising an antibody capable of specifically binding to said modified homocysteine to from an immunocomplex; and

(8) a third reagent capable of activating said protected alkylating reagent.

(d) measuring the amount of said immunocomplex, the amount thereof being related to the amount of homocysteine in said sample.

Claim 44 (amended). A method of determining the amount of homocysteine in a sample, wherein at least a portion of said homocysteine is in the free disulfide form, comprising the steps of:

(c) preparing an admixture comprising:

(6) said sample,

(7) a releasing agent to release said homocysteine from the disulfide form,

(8) an alkylating reagent having a haloketone or alpha haloaldehyde functional group, the carbonyl of said haloketone or alpha haloaldehyde functional group derivatized with a protected functional group capable of being activated to chemically modify the sulfhydrly groups of homocysteine to form modified homocysteine, and

(9) an antibody capable of specifically binding to said modified homocysteine to form an immunocomplex, and

(10) an activating reagent capable of deprotecting said protected functional group of said alkylating reagent; and

(d) examining said medium for the amount of said immunocomplex, the amount thereof being related to the amount of homocysteine in said sample.